LETTERS

Medial tibial stress syndrome due to methotrexate osteopathy

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Methotrexate (MTX) is a folate antagonist with well known side effects, which mainly include haematological and hepatic adverse events, and less frequently lung or bone toxicities. The use of MTX in high doses has been associated with an osteopathy, which is characterised by severe bone pain, osteoporosis, and insufficiency fractures of the legs.[1] We present two patients with rheumatoid arthritis (RA) who developed medial tibial stress syndrome (MTSS) while taking low dose MTX.

The first patient, a 69 year old woman, had a history of RA diagnosed in 2001.[2] After 1 year's treatment with MTX (10 mg/week), she reported a 1 month history of severe pain in the medial part of the left tibia. The pain had an acute onset, prevented her from walking, and was relieved by rest. A physical examination disclosed severe tenderness on the anterior and medial part of the lower third of the tibia. A simple *x* ray examination and bone scanning were normal. Magnetic resonance imaging (MRI) showed a linear abnormal high signal intensity along the medial surface of the tibia on T_2 weighted, fat suppressed, proton density fast spin echo images (fig 1). With the diagnosis of MTSS she was treated with rest for 6 weeks without improvement. In February 2003, MTX was withdrawn because of recurrent oral ulcers. One month later, she still had moderate left tibial pain and treatment was started with alendronate 70 mg/week. Within 1 week she was asymptomatic.

The second patient, a 61 year old woman, was diagnosed with RA[2] in May 2001. After 27 months' treatment with MTX (15 mg/week) she developed severe pain in the left tibia that prevented her from walking and was relieved by rest. A physical examination disclosed severe tenderness on the medial part of the tibia, especially on the lower third, with a mild oedema. MRI was compatible with the diagnosis of MTSS and based on the experience of the first patient, MTX was withdrawn and treatment with risedronate 35 mg/week was started. Within 1 week the patient was asymptomatic.

The presence of MTX osteopathy in patients with inflammatory conditions treated with low dose MTX has been reported but is still debated.[3–7] A critical review of published reports suggests that most patients treated with low dose MTX have no increased risk of MTX osteopathy.[8]

MTSS, a common condition of uncertain origin found in athletes, is characterised by pain in the distal posteromedial aspect of the tibia during exercise, with or without increased scintigraphic uptake in the affected region.[9 10] Although the exact cause of MTSS is unclear, changes in bone metabolism are likely to be involved. It has been shown recently that athletes with MTSS have a localised low bone mineral density. MRI is of high diagnostic value in differentiating MTSS and stress fracture. In MTSS MRI can visualise juxtaosseous oedematous and inflammatory reactions, and an increased signal would appear to be characteristic when the band-like image is fixed to the periosteum. The most effective treatment is considered to be rest, and despite appropriate treatment, patients with MTSS are usually symptomatic for a prolonged period. In our patients, the rapid resolution of the clinical syndrome was striking, suggesting that MTX treatment was related to MTSS and that biphosphonate treatment could also accelerate the resolution of the osteopathy.

In summary, we describe two postmenopausal women with RA who developed MTSS while receiving treatment with low dose MTX. Withdrawal of MTX and the addition of biphosphonates were followed by a rapid resolution of symptoms, suggesting a relationship between MTX and MTSS. We suggest that MTSS should be added to the clinical spectrum of MTX osteopathy.

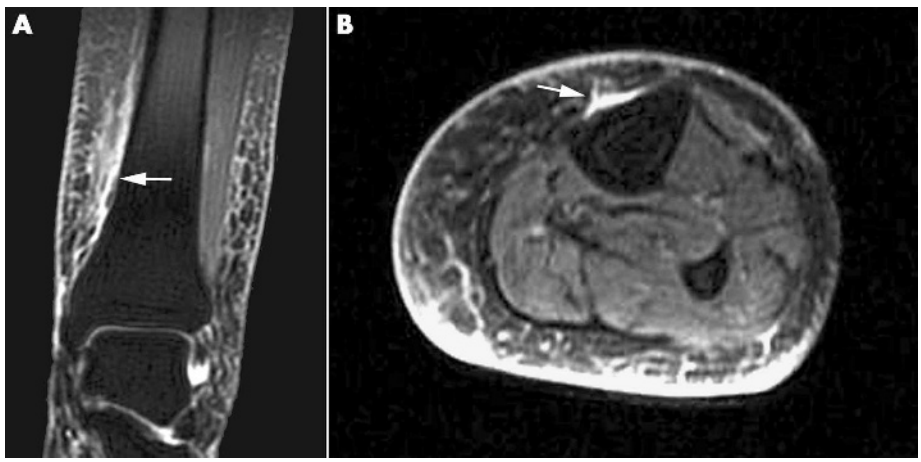

Figure 1 Magnetic resonance imaging of distal tibia. Coronal (A) and axial (B) fat suppressed, T_2 weighted, fast spin echo images show hyperintense signal intensity along the medial surface of the tibia corresponding with periosteal oedema (arrows). No cortical or marrow abnormality was demonstrated.

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Leflunomide and methotrexate combination therapy in daily clinical practice

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A few years ago, the immunomodulatory molecule leflunomide was licensed as a new disease modifying anti-rheumatic drug (DMARD) for the treatment of rheumatoid arthritis (RA). Several randomised clinical trials have established its safety and efficacy, which is comparable to that of sulfasalazine and methotrexate.[1 2] Some questions remain about the performance of this agent in current therapeutic strategies.[3] One particular important query about the applicability of leflunomide is its use in combination therapy with methotrexate. Although there have been some conflicting opinions, it was shown by van Riel and Weinblatt *et al* that such combination therapy is safe and more effective than treatment with leflunomide or methotrexate alone.[4 5] A major tool to confirm the usefulness of a drug in daily practice is a survival study. It informs clinicians about potential discrepancies with the results from randomised clinical trials, because patients included in a trial might differ from a real population in age, comorbidity, and atypical or refractory disease.

In this context, we examined the survival of leflunomide with or without concomitant methotrexate treatment in a Belgian clinical setting for a follow up period of 30 months. Our cohort consisted of 60 patients with RA with established disease and fulfilling the American College of Rheumatology classification criteria for RA.[6] According to their rheumatologist, treatment with classical DMARDs was insufficient in all patients. They were treated with leflunomide as part of a compassionate sampling programme, for which enrolment took place between August 2000 and April 2002 in the rheumatology departments of three Belgian Centres (St Augustinus Hospital Antwerp, University Hospital Ghent, Elisabeth Hospital Sijsele-Damme).

All patients received a loading dose of 100 mg leflunomide for three consecutive days. Afterwards, leflunomide was given at a dose of 20 mg/day, with or without methotrexate, and this according to the rheumatologist's decision. Forty of 60 patients received concomitant methotrexate from the start, at different doses. Twenty patients received leflunomide monotherapy. After 30 months, 37 (62%) of the 60 patients with RA were still receiving leflunomide treatment. In the groups with concomitant methotrexate and with leflunomide monotherapy 26/40 (65%), and 11/20 (55%), respectively, continued treatment (fig 1). Two major reasons for discontinuation were inefficacy and adverse events (respectively 18.3% and 15.0% at 30 months). The number and nature of adverse events were comparable in both groups and were mainly gastrointestinal (nausea, diarrhoea, raised liver enzymes), alopecia, anaemia, skin rashes, and hypertension. These side effects are consistent with those reported in previous studies.[1 2 5]

Another interesting observation is that whereas the leflunomide dosage remained stable during 30 months in the majority of the patients, the methotrexate dose was decreased in a substantial number of patients: it was reduced in 14 (35%) and even stopped in an additional 11 (27.5%) patients with RA. In contrast, it was increased in only four (10%) and remained stable in 11 (27.5%) patients with RA. This further supports the beneficial effect of combining both drugs.

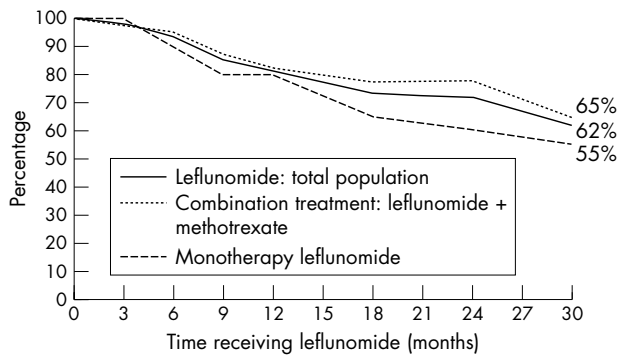

Figure 1 Treatment duration and the percentage of patients still receiving leflunomide after 30 months in the total leflunomide cohort and in the leflunomide cohorts with and without concomitant methotrexate.